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Review Article

The prevalence of kidney scarring due to urinary tract infection in Iranian children: a systematic review and meta-analysis

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Summary

Introduction
Urinary tract infection is one of the most common diseases in childhood, and can lead to severe complications such as renal scarring in case of lack of diagnosis and timely treatment.

Objective
The aim of this study was to investigate the prevalence of kidney scarring caused by urinary tract infection in Iranian children by meta-analysis.

Study design
English -language databases including Science Direct, PubMed, Scopus, Web of Science, and Springer, and Persian -language sites including SID, Magiran, Iranmedex, and Medlib, and the Google Scholar search engine were searched by in March 2018 using MeSH keywords. The heterogeneity of studies was studied using the I2 index. Data were analyzed using STATA software, version 15.1.

Results
In 18 studies, the prevalence of kidney scarring from urinary tract infections in Iranian children was 31% (95% confidence intervalCI: 22%—39%), (which was 14% in girls and 23% in boys. Also, the prevalence of kidney scar in children with urinary reflux was 47% and in children without urinary reflux was 12%. The most common symptom of the renal scar was fever in 61%, followed by urinary reflux in 45% (unilateral in 42% and bilateral in 30%). Also, the prevalence of mild, moderate, and severe reflux, respectively, was 31%, 27%, and 13%. Meta-regression also showed that the prevalence of kidney scar due to urinary tract infections had no significant relationship with the number of samples and years of research ($P > 0.05$).

Discussion and Conclusion
About one-third of Iranian children suffering from urinary tract infections had kidney scarring, so that the prevalence is lower in girls than in boys. Also, the prevalence of renal scarring in children with urinary reflux is about four times higher than that in children without urinary reflux.

Introduction

Chronic diseases are one of the most important health problems that lead to psychological, economic, and social problems [1]. Urinary tract infections are among the most common causes of child morbidity [2—5] and one of the most common bacterial diseases in children [6—8], with a relapse rate of 30—40% [9,10]. Urinary tract infections account for 1.1 to 7 million referrals per year [11,12]. It affects 5% of infants, 3%—5% of girls, and 1% of boys [7,8,13—15] so that at the age of 5 years, about 8% of girls and 1%—2% of boys suffer from urinary tract infections at least once [16]. The peak prevalence of this disease is observed in girls aged 2—3 years and occurs most often in boys in the first year of life. In children, especially in the first three months of life, urinary tract infections are more common in boys than in girls, but in other age groups, girls are more likely to be infected than boys [17]. The predisposing factors for urinary tract infections include sex (girls), uncircumcised boys, urinary tract disorder, vitamin D deficiency [18], diabetes, and constipation. Another predisposing factor for urinary tract infection is urinary reflux from the bladder, which increases the chance of developing kidney scarring [15,19,20]. Kidney scarring and permanent damage to the kidneys are the most common complication of urinary tract infection [5,15,21], which itself causes serious complications such as hypertension and chronic renal failure [22—26]. Renal scarring is a permanent and irreversible degeneration of the renal parenchyma. This condition

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Table 1 Information on articles entered into the systematic review process and meta-analysis.

Reference	Author	Type of study	Test for diagnosis of renal scar	Test for diagnosis of reflux	Time of DMSA (month)	Test for diagnosis of urinary tract infection	Age range	Year of study	City of study	Sample size	Prevalence of renal scar (%)
[67]	Ghane sherbaf.F	Cross-sectional	DMSA	VCUG	6	Analysis & urine culture	1 day to 15 years	2006	Mashhad	50	0.44
[47]	Ahmadzade.A	Cross-sectional	Sonography & DMSA	VCUG	4–6	Analysis & urine culture	2 months to 15 years	2000–2001	Ahvaz	126	0.04
[48]	Sorkhi.H	Cross-sectional	DMSA	VCUG	4–6	Urine culture	1 month to 15 years	2010	Babol	59	0.537
[68]	Hashemian.H	Cross-sectional	DMSA	–	6	Urine culture	1–14 months	2002–2003	Tehran	103	0.284
[69]	Akhavan Sepahi.M	Cohort	DMSA	–	6	Urine culture	1 month to 16 years	2004–2005	Qom	120	0.233
[70]	Sharifian.M	Cohort	DMSA	Beta-two microglobulins & VCUG	6	Urine culture	3 months to 12 years	1998	Tehran	53	0.41
[71]	Niki Bakhsh. AA	Cross-sectional	DMSA	VCUG	4–6	Urine culture	6 months to 14 years	2011–2013	Orumie	60	0.585
[46]	Sorkhi.H	Cross-sectional	DMSA	VCUG	4–6	Urine culture	1 month to 15 years	2001–2002	Babol	42	0.761
[72]	Bahrehmand.SH	Cross-sectional	DMSA	–	4–6	Urine culture	2 months to 12 years	2014	Yazd	400	0.03
[73]	Ghotbi.F	Cohort	Tc99,DMSA	VCUG	6	Urine culture	9 months to 14 years	1997–1998	Tehran	40	0.125
[26]	Sayedzadeh.SA	Cross-sectional	Sonography & DMSA	–	4–6	Urine culture		2014	Kermanshah	288	0.406
[74]	Sfaei asl.A	Cross-sectional	DMSA	VCUG	4–6	Urine culture	1–14 years	2004–2006	Rasht	128	0.21
[75]	Sharifian. M	Cross-sectional	DMSA	VCUG	4–6	Urine culture	4.5 ± 3.8 years	2013–2014	Qom	40	0.2
[76]	Ghane sharbaf.F	Cohort	DMSA	VCUG	4–6	Urine culture	54 days to 16 years	1985–2004	Mashhad	330	0.23
[77]	Mohammadjafari.H	Cohort	DMSA	VCUG	4–6	Urine culture	Under one year	2004–2012	Mazandaran	152	0.195

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may increase following urinary tract infection and high degrees of reflux [27—32].

The severity of the reflux is classified according to the international classification of reflux disease as grade 1 to 5 that the higher rate of reflux is associated with more likelihood of kidney damage [33]. The incidence of renal scarring and reflux nephropathy depends on the degree of reflux that children with a high grade of reflux are prone to urinary tract infections and such children are in turn at the elevated risk for pyelonephritis and renal scarring [19,34—38].

In fact, children are at higher risk for acute renal injury, and ultimately kidney scaring, compared with adults following urine infection [16].

About 15% of children with urinary tract infections develop renal scarring within one to two years after infection [6,39—41], and the chance of scarring increases with any new infection [42]. Considering the difference in the reported incidence of renal scar caused by urinary tract infection in Iranian children, the current systematic review and meta-analysis can provide necessary information for both physicians and public health policy makers.

Materials and methods

Protocol study

The present study is a meta-analysis on the prevalence of kidney scarring caused by urinary tract infections in Iranian children. In this study, the preferred reporting items for systematic review and meta-analysis (PRISMA) protocol [43] was used for systematic review and meta-analysis.

Search strategy

In order to obtain the required resources, English language databases including ScienceDirect, PubMed, Scopus, Web of Science and Springer and Persian language databases including SID, Magiran, Iranmedex and Medlib plus Google Scholar search engine were searched without time limit using the valid keywords of 'renal scarring, urinary tract infection, urinary reflux, children, Meta-Analysis and Iran ' and related Latin and MeSH equivalent. Their combinations were also searched using (AND, OR) operators in English language bases. The documents found were for the period from December 1995 to March 2018.

Inclusion and exclusion criteria

The studies included in the study investigated the prevalence of kidney scar caused by urinary tract infection in Iranian children. For the purpose of this study, we excluded those studies conducted outside of Iran, those that survey the prevalence of kidney scar in adults, those with non-random sampling methods such as easy sampling and quota sampling, those with no report of required information such as number of samples or outbreak of renal scars, those with a score lower than 14 according to the Newcastle—Ottawa Scale (NOS) checklist (score lower than 14), and finally, we excluded those studies if the full text were not available [44] (Chart 1).

Qualitative assessment of studies

In order to evaluate the quality of studies, the NOS was used and the cutoff point of the studied was considered score 4. The NOS contains eight items, categorized into three dimensions including selection, comparability, and—depending on the study type—outcome (cohort studies) or exposure (case—control studies). For each item, a series of response options is provided. A star system is used to allow a semi-quantitative assessment of study quality, such that the highest quality studies are awarded a maximum of one star for each item with the exception of the item related to comparability that allows the assignment of two stars. The NOS ranges between zero and nine stars[44]. Two researchers independently assessed all the articles, and if there was an inconsistency between them, the third researcher decided about the quality score.

Extracting the data

Two researchers independently performed data extraction from studies to minimize bias in reporting and data collection errors. Researchers entered the extracted data, including the name of the researcher, the study title, the number of samples, the year and place of the research, the total prevalence of kidney scar, the prevalence of kidney scar in girls and boys, the prevalence of urinary tract reflux, the incidence of unilateral and bilateral urinary refluxes, and the incidence of fever, in a checklist.

Statistical analysis

The variances of each study were calculated using the binomial distribution formula. In order to study the heterogeneity of the studies, Cochran Q test and I^2 index were evaluated that I^2 between 25% and 75% indicated moderate heterogeneity and more than 75% indicated high heterogeneity[45]. Data were analyzed using STATA software, version 15.1. The meta-regression was used to show the association between the prevalence of kidney scaring caused by urinary tract infections in Iranian children with the number of samples and years of research. The significance level of the tests was considered to be $P < 0.05$.

Results

In 18 studies, 15 studies had examined the prevalence of kidney scar on the basis of the number of patients (Table 1) and 3 other studies, the prevalence of the renal scar on the basis of the number of kidney units (Table 3). The data of the articles examined are shown in tables [1,3] and processes for the inclusion of studies in the meta-analysis are shown in Fig. 1. In this meta-analysis, the prevalence of kidney scar from urinary tract infections in Iranian children was 31% (girls 14% and boys 23%). The prevalence of the kidney scar in children with urinary reflux was 47% and in children without urinary reflux was 12%. Common symptoms of kidney scar in

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children with urinary tract infection included fever in 61%, urinary reflux in 45%, unilateral urinary reflux in 42%, and bilateral urinary reflux in 30%. Also, the prevalence of mild, moderate and severe reflux, respectively, was 31%, 27%, and 13% ((Table 2). In three studies that examined kidney scar in children based on the number of kidneys, the prevalence of the renal scar in children was 43% (95% confidence interval [CI]: 65% −20%). According to Figs. 2 and 3, there is no significant relationship between the prevalence of renal scars and the number of samples and years of research in children with urinary tract infection. Sensitivity analysis showed that with the elimination study of Sorkhi and Hashemi [46], in 2001, the prevalence of kidney scarring from urinary tract infections in Iranian children ranged from 31% to 27.3% (95% CI: 18.6%–36%), and eliminating the study by Ahmadzade et al. [47], in 2000, revealed that kidney scarring from urinary tract infections decreased to 32.6% (95% CI: 21.9%–43.3%). Sensitivity analysis shows that these two studies are the most influential studies in the final result of the current research (Fig. 4).

Discussion

The prevalence of kidney scarring from urinary tract infections in Iranian children was 31% (girls 14% and boys 23%). Of all three children with urinary tract infections, a child is affected by kidney scarring, which is 1.5 times higher in boys than in girls. The prevalence of the renal scar in children with urinary reflux was 47% and in children without urinary reflux was 12%.

We find that the prevalence of kidney scar in children with urinary tract reflux is approximately 4 times higher than that of children without urinary reflux, and there is a significant difference between the two groups. It can be said that urinary reflux increases the risk of kidney scarring in children four times, and urinary reflux is a serious risk factor for kidney scarring.

Common symptoms of kidney scar in children with urinary tract infection included fever in 61%, urinary reflux in 45%, unilateral urinary reflux in 42%, and bilateral urinary reflux in 30%.

Because urine reflux is of two types (unilateral and bilateral), we analyzed the type of urinary reflux and found that the prevalence of unilateral urinary reflux is 1.5 times higher than bilateral urinary reflux in Iranian children.

Also, the prevalence of mild, moderate, and severe reflux, respectively, was 31%, 27%, and 13%.

Regarding the results of this study, with regard to the grading of urinary reflux in the three levels of mild, moderate, and severe, most Iranian children suffer from mild reflux so that the prevalence of mild reflux among children with urinary tract infection is about three times higher than that of severe reflux. In an analysis based on the number of kidneys of children with urinary tract infections, the

Table 2 Prevalence of kidney scar and symptoms of urinary tract infection in Iranian children according to the subgroups examined.

Subgroups		Number of study	Prevalence (95% CI)	*P*-value	I^2 (%)
Overall		15	31% (21%–40%)	<0.001	97.3
Reflux	The prevalence of renal scarring in children with reflux	3	47% (15%–80%)	<0.001	96.6
	The prevalence of renal scarring in children without reflux	3	12% (0%–24%)	<0.001	94.1
	The prevalence of reflux in children	8	45% (34%–57%)	<0.001	89.6
	The prevalence of unilateral reflux	5	42% (24%–61%)	<0.001	96.3
	The prevalence of bilateral reflux	5	30% (12%–48%)	<0.001	97.2
	The prevalence of mild reflux	2	31% (3%–59%)	<0.001	97.3
	The prevalence of moderate reflux	3	27% (13%–41%)	<0.001	94.9
	The prevalence of severe reflux	3	13% (1%–25%)	<0.001	96.7
Sex	The prevalence of renal scarring in girls	3	14% (0%–34%)	<0.001	97.9
	The prevalence of renal scarring in boys	3	23% (0%–62%)	<0.001	96.6

CI, confidence interval.

Table 3 The data of the articles studied in the field of kidney scar on the basis of the number of kidneys.

Reference	Author	Type of study	Test for diagnosis of renal scar	Test for diagnosis of reflux	Time of DMSA (month)	Test for diagnosis of urinary tract infection	Age range	Year of study	City of study	Sample size	Prevalence of renal scar (%)
[48]	Sorkhi.H	Cross-sectional	DMSA	VCUG	4–6	Urine culture	Under one year	2007–2008	Babol	71	0.388
[78]	Jalili.M	Cross-sectional	Sonography & DMSA	–	4–6	Urine culture	–	2010	Kermanshah	60	0.65
[79]	Fahimi.D	Cohort	DMSA	VCUG	6	Urine culture	1 month to 12 years	1995–1998	Tehran	50	0.25

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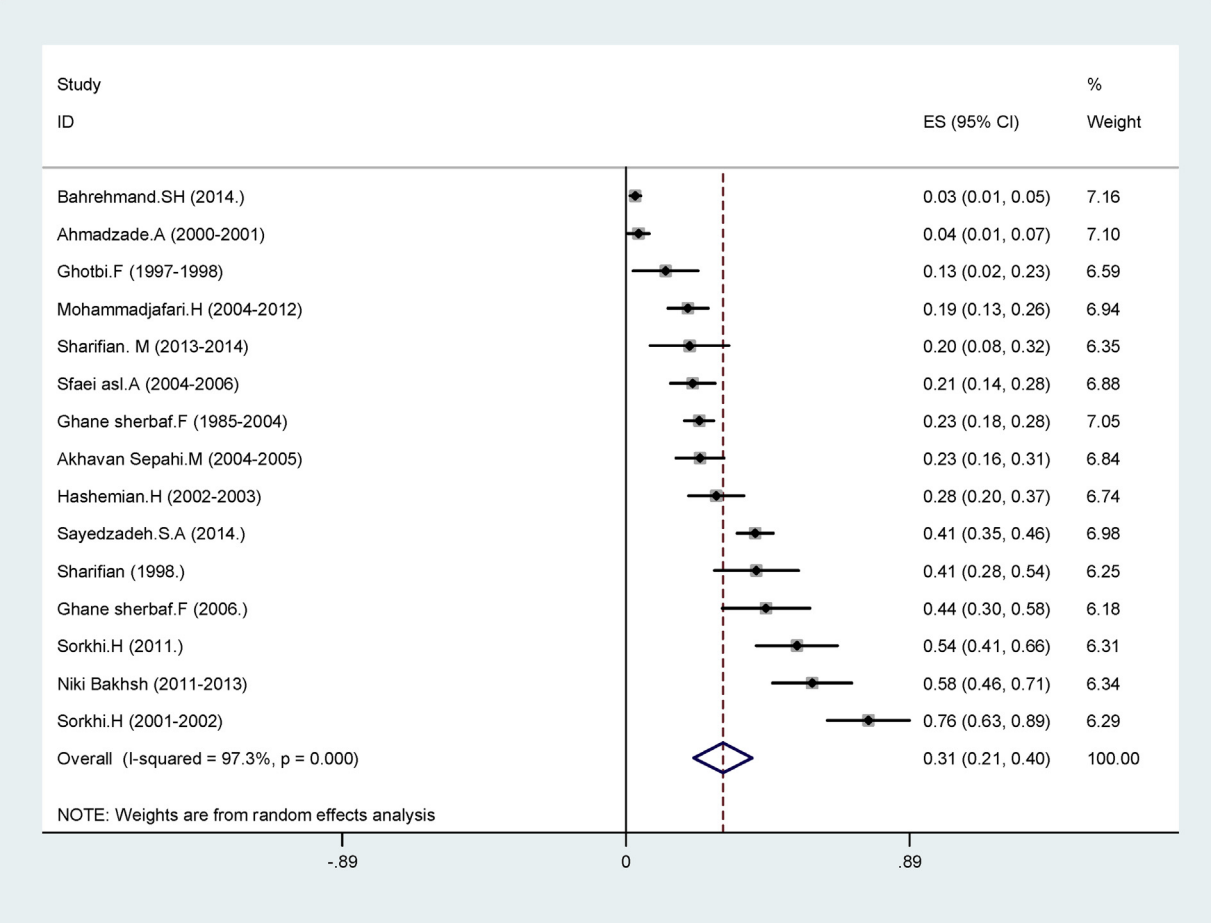

Fig. 1 The prevalence of kidney scar from urinary tract infections in Iranian children with 95% confidence interval, based on the author's name and year of research. ES, effect size; CI, confidence interval.

prevalence of the renal scar in children was 43%. That is, from almost tow kidney, a kidney affects the renal scar caused by urinary tract infection.

According to Fig. 2, there is no significant relationship between the prevalence of the renal scar and sample size ($P = 0.166$). This chart is a descending trend and shows that as more specimens are found, the prevalence of renal scarring in children with infections is reduced, but because $P > 0.05$, this relationship is not significant. That although with increasing sample size, the prevalence of urinary tract infection in Iranian children is decreasing.

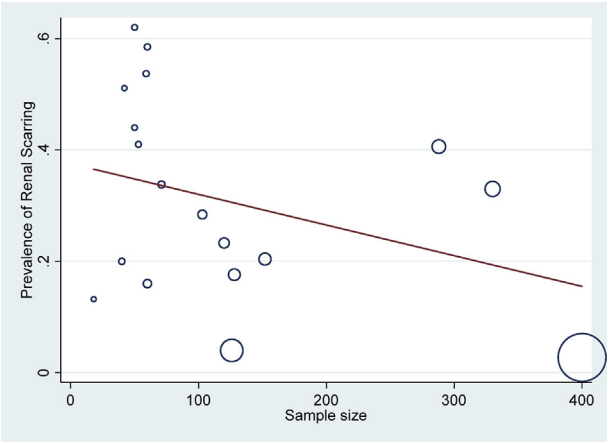

Fig. 2 Relationship between the prevalence of kidney scar from urinary tract infections in Iranian children and the number of research samples using a meta-regression model.

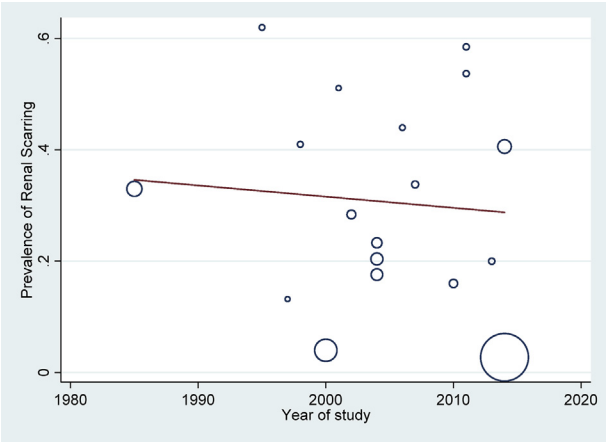

Fig. 3 Relationship between the prevalence of kidney scar from urinary tract infections in Iranian children and the year of research using a metastasis model.

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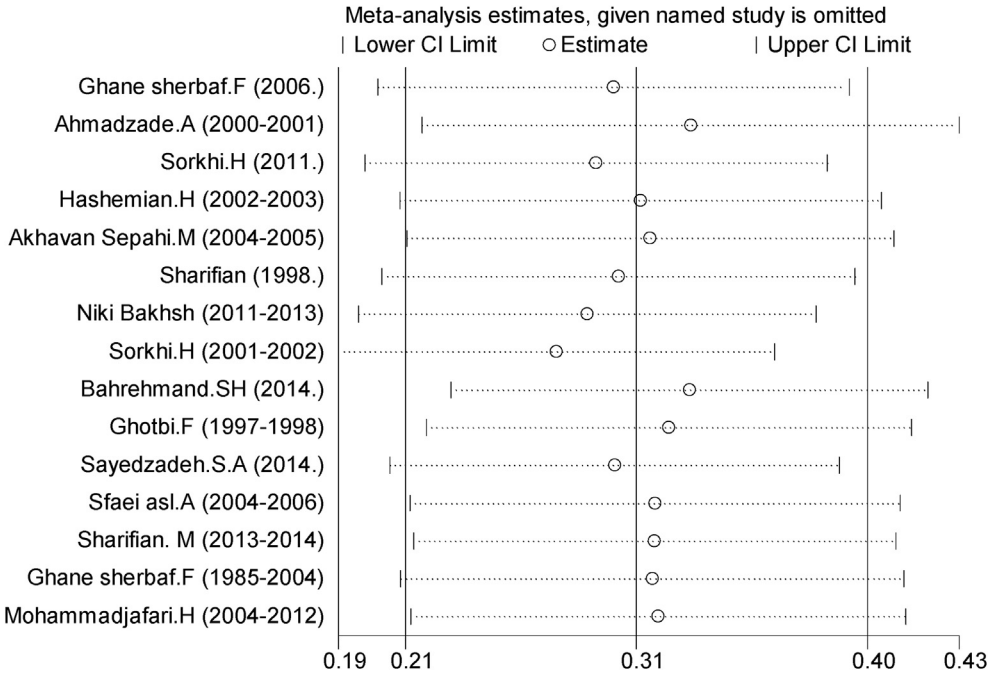

Fig. 4 Sensitivity analysis. CI, confidence interval.

As shown in Fig. 3, there is no significant relationship between the incidence of the renal scar and the year of the study (P = 0.735). In other words, during the years studied from 1995 to 2018, the prevalence of renal scarring due to urinary tract infection in Iranian children slow down slightly, but this decline is not statistically significant.

Several reports have been presented on the association of urinary reflux with renal scaring; as reported in the nephrology children's journal (2004), the rate of renal scarring based on reflux ranged between 5% and 50% [20] as 30%–55% of children at the time of diagnosis of urinary tract reflux have scars in the kidney parenchyma [7,48–50]. In the study by Doganis et al. [51], during a 5-year period, 278 infants aged less than 12 months, who were diagnosed with the first proven urinary tract infection, had renal scar in 64% of children in the urinary reflux group and 44% in the non-urinary reflux group that was consistent with our survey.

In a study on 1221 children who were assessed by a non-selective sampling method and after the appearance of the first symptom of urinary tract infection, 74 children had renal scarring in the IVP with a significant difference between 21 boys and 53 girls with renal scarring [52] that was not in line with our results. But in Howard et al. [53] study in Hong Kong, the overall prevalence of renal scars in male and female children with urinary tract infection aged less than 5 years was 18% and 11%, respectively, which is consistent with the results of the present study. In a study by Barry et al. [54], in 1998 in the UK, it was found that of 648 children with a mean age 3.89 years, 15.9% had kidney scarring due to urinary tract infection.

In another study in England, Christian et al. [13] showed that of 990 children with urinary tract infections, 8.5% had renal scarring. In the UK, Smellie et al. [55] studied 111 children younger than 12 years and found that 17.1% of those had kidney scarring due to urinary tract infections. In a study by Moorthy et al. [56] in England between 2002 and 2003, of the 216 children younger than 1 year who had urinary tract infections, 3.7% of infections resulted in kidney scarring. In a study by Miller and Phillips, in 1981, the lack of treatment protocol led to a renal scaring in 27% of patients [57]. In total, the prevalence of renal scarring was lower in the pointed studies than in the present study.

In the United States, Naseer and Steinhardt [58] in 1988 examined 1426 children and stated that 13.5% of children after a urinary tract infection suffer from kidney scarring. In the United States, Hoberman et al. [59] examined 309 children younger than two years and found that 9.5% had kidney scars. A study in the United States between 2007 and 2011, conducted by keren et al. [60] on 400 children, concluded that the prevalence of kidney scar in children with urinary tract infection was 8%. In the United States of America in 2016, Shaikh et al. [61] found that of 482 children younger than 6 years, 7.2% had kidney scars. In another study, Mattoo et al. [62] in the United States examined 599 children younger than 6 years and found that 10% of children had kidney scarring.

In Taiwan, Lin et al. [63] monitored 314 patients between 1996 and 1999 and found that 11.1% of them had kidney scarring due to urinary tract infections. In a study conducted on children with urinary tract infection younger than one year, scars were observed in 38.8% of the kidneys due to vesicoureteral refluxes [48]. In 1974, Shah et al. [49] conducted a study on 105 English children and reported that 45.7% of them had kidney scarring due to urinary tract infections. In Italy in 2005, Bressan et al. [50] reported that 34 of 41 children younger than 3 years who had a urinary tract infection suffered from kidney scarring.

In another study in England, Scott and Stansfeld [64] examined 201 children with urinary tract infections and found that 42% had kidney scar. In a study by Montini et al. [65] in Italy between 2000 and 2005, of 300 children younger than 2 years, 15% had renal scarring. Wennerstrom

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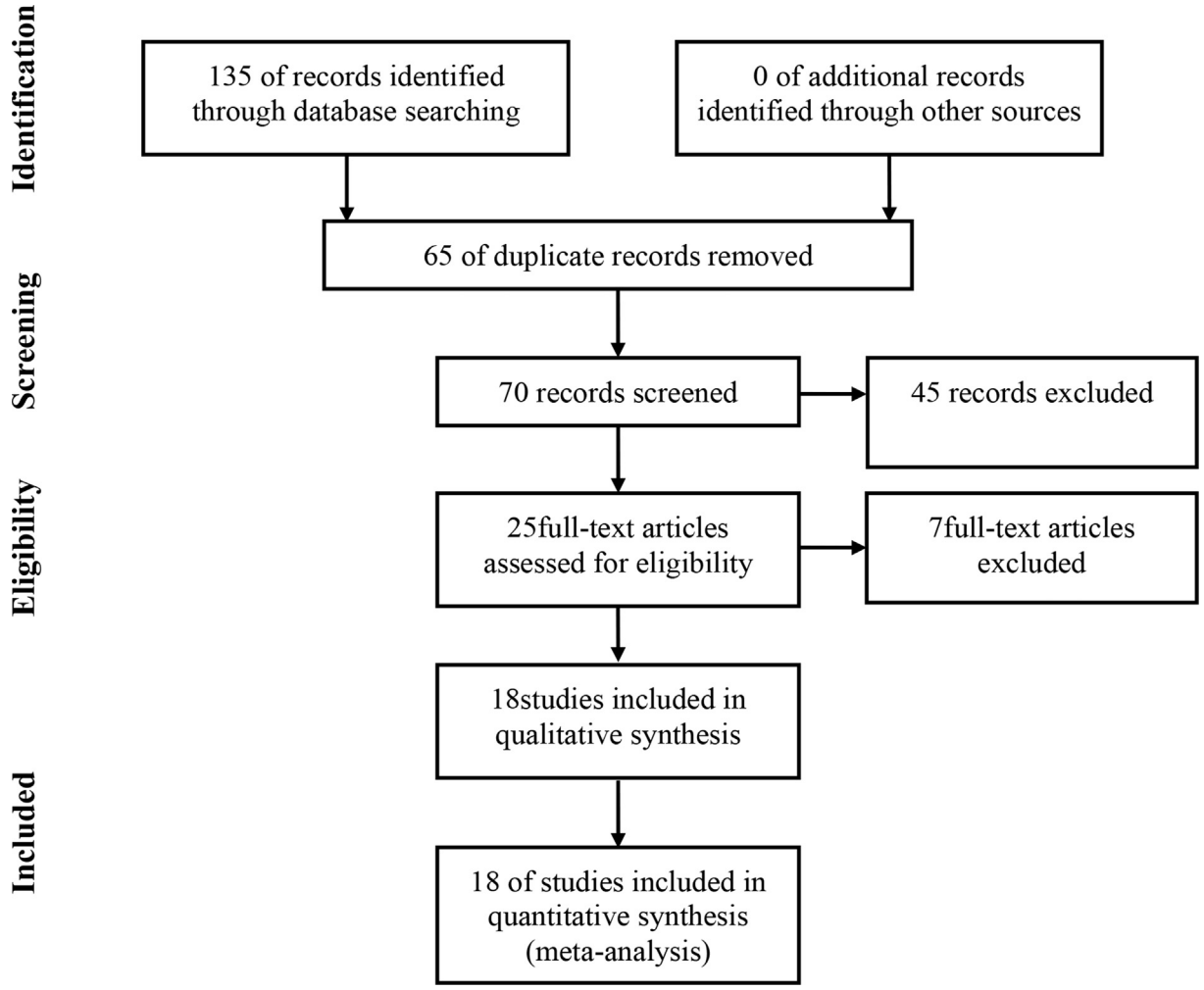

Chart 1 Processes for the inclusion of studies into the systematic review and meta-analysis based on PRISMA

et al. [66] in Sweden in a study on 1221 people found that 6.1% of children with urinary tract infections suffered kidney scarring. In the aforementioned studies, the prevalence of renal scarring is greater than the present study.

Limitations of study

One of the limitations of the study is the lack of reports of the prevalence of kidney scar in children with urinary tract reflux by gender, the absence of a study on children in the south of the Iran that led to no estimates of the prevalence of kidney scarring caused by urinary tract infections in children in this area. Given that some studies did not elaborate a precise age group for the children surveyed, we could not make a breakdown of the children's age group. Unequal Distribution of Studies in Different Regions of Iran. Unequal Distribution of Sample size Between Girls and Sons.

Conclusion

The prevalence of kidney scarring due to urinary tract infection in Iranian children is high so that one-third of children suffer from kidney scarring due to urinary tract infections. Also, the results of the study show the prevalence of kidney scar in girls is lower than that in boys and the prevalence of renal scarring in children with urinary tract reflux is about four times higher in children without urinary reflux, with urinary reflux approximately four times the risk of renal scarring so that urinary reflux almost quadruples the risk of renal scarring. Meta-regression showed that the prevalence of kidney scarring from urinary tract infections in Iranian children has not decreased in recent years. Therefore, parents and officials should pay more attention to prevention and control of urinary tract infections in children, before causing kidney scarring and other abnormalities.

Author statements

Ethical approval

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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Competing interests

The authors declared no competing interests.

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